

Researchers reveal underlying mechanism of powerful chemotherapy for prostate cancer treatment

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The power of taxane-based chemotherapy drugs are misunderstood and potentially underestimated, according to researchers at Weill Cornell Medical College in the September 15 issue of the journal *Cancer Research*.

Most physicians and investigators believe that taxane chemotherapy (paclitaxel, [docetaxel](#) and cabazitaxel) just does one thing—stop a cancer cell from dividing—but the team of Weill Cornell scientists have revealed it acts much more powerfully and broadly, especially against [prostate cancer](#).

"Taxanes are one of the best class of chemotherapy drugs that we can use to treat our cancer patients, but while they are effective against a wide range of tumors, they don't work in all of them, and often patients become resistant," says the study's senior investigator, Dr. Paraskevi Giannakakou, an associate professor of pharmacology in medicine and pharmacology and director of laboratory research for the Division of Hematology and Medical Oncology at Weill Cornell. "However, our new understanding of the precise action of taxanes in a cancer cell may help us overcome drug insensitivity or acquired resistance to the drugs and design therapies that can be used in combination with them to improve [cancer control](#)."

In their study, the researchers stress that investigators must shift their

attention away from taxane's function during [cell division](#) to the drugs' effects on halting the everyday movement of proteins and protein-to-protein communication within cancer cells—and to understanding how and why a cancer cell can still survive. Researchers suggest that cancers that are insensitive to taxanes—or those that have become resistant to them—may, for example, switch to alternate forms of "transportation" to shuttle proteins within cells in a way that does not depend on the cell's [skeletal structure](#) which is the target of taxane therapy.

Researchers showed in the study that the [androgen receptor](#) (AR), which is a driving force in prostate cancer growth and metastasis, "moves" along microtubules to be transported to the nucleus. When a taxane binds microtubules, it stops AR from traveling, thus inhibiting its activity. Taxane [chemotherapy drugs](#) such as paclitaxel, docetaxel and cabazitaxel work by binding tubulin, a protein that makes up microtubules. Microtubules are the rope-like channels that provide both a skeletal structure to cells as well as provide "highways" along which molecules, such as proteins, RNA complexes and vesicles, can travel from one part of the cell to another and interact with each other.

"Microtubules are the highly dynamic network of wires within cells, and when taxanes are used, the network stops moving," says Dr. Giannakakou. This is best observed when cancer cells attempt to divide, she says. "It is easy to see in the laboratory, that prostate cancer cells double every 30-48 hours, and taxane stops them from doing that, which pushes these cells to die. This leads everyone to think that this is exclusively how taxanes work – they stop cells from dividing."

But Dr. Giannakakou and her research team point out in their new study that patients have significantly lower rates of cell division in their tumors than do cancer cells growing in the lab. In fact, [cancer cells](#) in prostate [cancer patients](#) only divide every 33-577 days, she says. "Thus, the therapeutic benefit of taxanes on microtubules depends on more than

just stopping cell division."

The new insights provided by this study about the action of taxanes on AR trafficking helps explain the clinical activity of these drugs in the treatment of prostate cancer while at the same time can help researchers better understand why an individual patient might respond or not to taxane therapy. Such insights are critical for future chemotherapy customization, according to researchers.

The drug that was later named Taxol (paclitaxel) was isolated from the bark of a Pacific yew tree by federal researchers in 1967 and was later synthesized. In 1993 it was approved for use in ovarian cancer, and has since been used for lung, breast, head and neck and other cancers. Taxotere (docetaxel), synthesized from chemicals extracted from the European yew tree, was developed as an alternative to Taxol, and is used for the treatment of many of the same cancer types. Cabazitaxel, the newest taxane, is a semi-synthetic paclitaxel analog and is used to treat patients with prostate cancer who have failed prior docetaxel chemotherapy.

"In the 20 years since Taxol was approved, hundreds of labs worldwide are trying to understand how taxanes work to stop cell division in cancer," Dr. Giannakakou says. "However, we think they need to now take a fresh approach and look at what these drugs do during the normal life cycle of a [cancer](#) cell and target the newly revealed underlying mechanisms and modes of movement with novel therapies, in combination with taxane therapy, to provide life-saving therapy for patients who don't benefit from taxanes."

Investigators working with Dr. Giannakakou on the study are the first author Maria Thadani-Mulero, who is a graduate student enrolled at Surrey University, UK performing her thesis work in Dr. Giannakakou's laboratory, and Dr. David M. Nanus, the Mark W. Pasmantier Professor

of Hematology and Oncology in Medicine and chief of the Division of Hematology and [Medical Oncology](#) at Weill Cornell.

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